

Repair of Conus Medullaris/Cauda Equina Injury using Human ES Cell-Derived Motor Neurons

Grant Award Details

Repair of Conus Medullaris/Cauda Equina Injury using Human ES Cell-Derived Motor Neurons

Grant Type: Early Translational II

Grant Number: TR2-01785-A

Project Objective: The PI is planning to determine whether acute or delayed transplantation of human ES cell-derived motor and autonomic neurons and neuronal precursors into the rat lumbosacral spinal cord can replace lost motoneurons and PPNs and reinnervate the lower urinary tract after a lumbosacral ventral root avulsion injury and surgical root replantation. If successful, our studies may result in a new treatment strategy to restore bladder function in subjects with CM/CE injuries, a vastly underserved patient population.

Investigator:

Name: leif Havton

Institution: University of California, Irvine

Type: PI

Disease Focus: Neurological Disorders, Spinal Cord Injury

Human Stem Cell Use: Embryonic Stem Cell

Award Value: \$1,527,011

Status: Closed

Progress Reports

Reporting Period: Year 1

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Reporting Period: Year 3

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Grant Application Details

Application Title: Repair of Conus Medullaris/Cauda Equina Injury using Human ES Cell-Derived Motor Neurons

Public Abstract: Injuries to the spinal cord commonly result from motor vehicle accidents, traumatic falls, diving, surfing, skiing, and snowboarding accidents, other forms of sports injuries, as well as from gunshot injuries in victims of violent crimes. Injuries to the anatomically lowest part of the spinal cord, the lumbosacral portion and its associated nerve roots commonly cause paralysis, loss of sensation, severe pain, as well as loss of bladder, bowel, and sexual function. Lumbosacral injuries represent approximately one-fifth of all traumatic lesions to the human spinal cord.

As a result of the direct injury to the lumbosacral portion of the spinal cord, there is degeneration and death of spinal cord nerve cells, which control muscles in the legs as well as bladder, bowel, and sexual function. No treatments are presently available in clinical practice to reverse the effects of these devastating injuries.

In order to reverse the loss of function after lumbosacral spinal cord injury, replacement of the lost nerve cells is required. Recent research studies have identified some properties that are shared by spinal cord neurons responsible for muscle and bladder control. Human embryonic stem cells can now be prepared in research laboratories to develop properties that are shared between nerve cells controlling muscle and bladder function. Such nerve cells are particularly at risk of degeneration and death as a result of injuries to the lumbosacral spinal cord. Human embryonic stem cells, which have undergone treatment to obtain properties of muscle and bladder controlling nerve cells, are now very attractive development candidates for new cell replacement therapies after lumbosacral spinal cord injuries. The proposed feasibility studies will study the properties of such cells in a clinically relevant rat model for lumbosacral spinal cord injuries.

In Specific Aim 1, we will determine whether ACUTE transplantation of human embryonic stem cells, which have been treated to develop properties of specific lumbosacral spinal cord neurons, may replace lost nerve cells and result in a return of bladder function in a rat model of lumbosacral spinal cord injury and repair.

In Specific Aim 2, we will determine whether DELAYED transplantation of human embryonic stem cells, which have been treated to develop properties of specific lumbosacral spinal cord neurons, may replace lost nerve cells and result in a return of bladder function in a rat model of lumbosacral spinal cord injury and repair.

A variety of functional studies will determine the effect of the cell transplantation on bladder function, walking, and pain. We will also use detailed anatomical studies to determine in microscopes whether the transplanted cells have grown processes to connect with pelvic target tissues, including the lower urinary tract. If successful, the proposed experiments may lead to a new treatment strategy for patients with lumbosacral spinal cord injuries.

Statement of Benefit to California:

There are presently about 250,000 patients living with neurological impairments from spinal cord injuries (SCIs) in the United States, and approximately 11,000 new cases present every year. SCIs typically result in paralysis, loss of sensation, pain as well as bladder, bowel, and sexual dysfunction. No successful treatments are available to reverse the neurological deficits that result from SCI. Common causes for SCIs include car and motorcycle accidents, skiing, diving, surfing, and snow boarding injuries, traumatic falls, sports injuries, and acts of violence. California medical centers encounter a large proportion of the overall cases in the U.S. because of our large population, extensive network of freeways, and an active life style with recreational activities taking place both along the Californian coastline and in the mountains.

The proposed development candidate feasibility project will capitalize on recent progress in human stem cell science and surgical repair of conus medullaris/cauda equina (CM/CE) forms of SCI. Human embryonic stem cell-derived neurons and neuronal progenitors, which express the transcription factor Hb9, will be transplanted into the conus medullaris in attempts to replace lost motor and autonomic neurons after a lumbosacral ventral root avulsion injury in rats. Surgical replantation of avulsed lumbosacral ventral roots into the spinal cord will also be performed in this clinically relevant model for CM/CE injury and repair.

If successful, our development candidate may reinnervate muscles and pelvic organs, including the lower urinary tract after CM/CE forms of SCI. Return of functional bladder control represents one of the absolute top priorities among the spinal cord injured population (Anderson, J Neurotrauma, 2004; 21, 1371-83). Successful recovery of bladder function after SCI is expected to have very significant impact on the quality of life of spinal cord injured subjects and markedly reduce health care costs.

Recovery of bladder function in spinal cord injured subjects would markedly reduce or eliminate the need for intermittent bladder catheterizations and indwelling bladder catheters. The number of visits in physicians' offices and already over-crowded California emergency rooms for bladder infections and other complications would be markedly reduced, thereby significantly reducing health care costs for both patients and our state. Improved neurological function among the SCI population is also expected to reduce care giver needs, thereby further reducing health care costs. The increased independence that will result from improved bladder control and concomitant possible recovery of other neurological functions, for instance in transfers and locomotion, will promote return to and participation in the work force for many individuals with SCI. These effects are also expected to bring a very positive effect to the California economy and increased quality of life for those living with an SCI.

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